WESTAT
CTSU WORK PROCEDURES

Work Procedure Number: CTSU 7.1
Title: CTSU Auditing Procedures
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I. PURPOSE

The purpose is to document the procedures for monitoring clinical trials for all CTSU enrollments, as well as facilitate coordination of CTSU-enrolled patient cases into the adult Cooperative Group audit mechanism. The objectives are to assure compliance with Federal regulatory requirements and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity.

II. SCOPE

This procedure applies to all cancer protocols approved by NCI/CTEP that have patient enrollment through the CTSU.

III. RESPONSIBILITY

All staff in the CTSU and Cooperative Group Audit Coordinators who perform clinical site monitoring activities are responsible for complying with the Work Procedures. Project Directors and their designees are responsible for assuring compliance with the Work Procedure.

IV. REFERENCES

Code of Federal Regulations: Title 21, Parts 50, 54, 56, 312 and 314. "FDA Regulations related to Good Clinical Practice and Clinical Trials".

Office for Human Research Protection (OHRP) of the Health and Human Services (HHS), Code of Federal Regulations Title 45, part 46.

NCI/CTEP Clinical Trials Monitoring Branch Audit Guidelines, Sections 3, 4, 5 & 6 for Cooperative Groups and Clinical Community Oncology Programs (CCOP) Research Bases and CTSU (version date Aug. 2001) at http://ctep.cancer.gov/monitoring/guidelines.html

V. DEFINITIONS

See CTSU Glossary for the following definitions:

Audit Information System (AIS)
Aligned Site
Audit Coordinator
CTSU Independent Clinical Research Sites (CICRS)
Clinical Trials Monitoring Branch (CTMB)
Drug Accountability Record Forms (DARFs)
Endorsed Study
Expanded Participation Project (EPP)
Institutional Review Board (IRB)
Non-Endorsed Study

VI. PROCEDURE

1. **Background Information**: The CTSU audit procedures are based on the Clinical Trials Monitoring Branch (CTMB)/Cancer Therapy Evaluation Program (CTEP) Guidelines (version date Aug 2001). The procedure will encompass all patient enrollments via the CTSU. The responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU.
    a) There are two distinct classes of institutions participating with the CTSU. The first are institutions that are members of an adult Cooperative Group, and the second are sites participating in the CTSU Independent Clinical Research Sites (CICRS) program.
    b) This SOP will outline the audit procedures for both types of sites.

2. **Audit Obligations for Patients Registered Through CTSU**: For group aligned sites, the audit of a patient registered through the CTSU is the responsibility of the group receiving credit for the enrollment. It will be vital for the CTSU Audit Coordinators to work directly with the Cooperative Group Audit Coordinator and Statistical Centers to manage the CTSU Audit Program. The CTSU obligations will vary based on the following scenarios:

CATEGORIES	TASKS	RESPONSIBILITY
CTSU to CTSU Enrollment	Conduct the audit and all associated tasks: ▪ Selection of sites ▪ Scheduling audit dates with site ▪ Scheduling auditors ▪ Selecting protocol cases ▪ Data Points ▪ Reporting requirements ▪ Providing follow up information	▪ CTSU responsible for all aspects of the audit.
CTSU to	▪ Conduct audit of endorsed	▪ Credited Group is responsible

Credited Group Endorsement	CTSU enrollment - **Group** ▪ Include CTSU cases in the regular Group audit	for all aspects of the audit. ▪ CTSU will provide a list of endorsed cases for the Group to use for case selection.
CTSU to Credited Group Non-Endorsed Enrollment	▪ Conduct audit - **Group** ▪ Facilitate the selection of CTSU cases - **CTSU** ▪ Provide the Group with the necessary tools, i.e., CTSU site accrual reports and other audit tools – **CTSU** ▪ Provide additional audit staff if indicated - **CTSU**	▪ Credited Group will perform the audit and associated tasks. ▪ CTSU will assist as described.
Group to Group Enrollment	▪ Conduct the audit and perform all associated tasks	▪ As per current practice, the Group is responsible for all aspects of the audit.
Group to Intergroup	▪ Conduct the audit and perform all associated tasks	▪ As per current practice, the Group for which the site is a member is responsible for all aspects of the audit.

Copies of CTSU protocols, audit checklists, audit worksheets [*Exhibit 7.1.1*], patient lists and other relevant audit tools will be made available to Cooperative Group Auditors for CTSU cases.

3. **Timing of Audits:** Based on CTMB guidelines, all new member main institutions will be audited within 18 months following entry of their first patient in NCI-sponsored treatment protocols, regardless of the mechanism of enrollment. A new affiliate institution may be audited when the Cooperative Group conducts the audit of the main member institution at 36 months.
    a) Following the initial audit, all institutions will be audited at least every 36 months and are at risk for audit during any one-year. Institutions remain at risk for audit even if their membership in the Cooperative Group is withdrawn or terminated, since they have made a commitment to long-term follow-up of patients on study, with provision of good quality data according to the study schedule.
    b) Selection of terminated institutions for audit is at the discretion of the CTSU, and focuses on institutions that had a large accrual, particularly to important or pivotal studies and/or a large number of patients in active follow-up.
    c) CICRS sites will be audited at least once every 36 months.

4. **Evaluation Components:** The CTSU on-site audit consists of reviewing and evaluating three components independently with compliance to CTMB and NIH guidelines for the conduct of clinical trials. The three components are as follows:

a) IRB documentation and informed consent content
b) Accountability of investigational agents and pharmacy operations
c) Individual patient case records

5. **Site Selection:** CTSU Audit Coordinators will use the Clinical Trials Monitoring Branch (CTMB) Audit Information System (AIS) to identify which institutions are due for audit and re-audit.

- **For Group-affiliated sites**: CTSU Audit Coordinators will communicate with Cooperative Group Audit Coordinators. CTSU will assist the Groups in identyfying enrollment of CTSU patients at the sites by making CTSU accrual reports available. CTSU will provide a list of endorsed cases for the Group to use for case selection [*Exhibit 7.1.2*). CTSU will select and list the non-endorsed cases for the Group [*Exhibit 7.1.3*].

- **For CICRS**: CTSU will coordinate the entire audit process. CTSU will enter audit date information into CTMB AIS at least 10 weeks prior to audit. CTSU will provide notice of CTSU audit to the audit site, at least 8 weeks in advance of the audit date.

6. **Selection of CTSU Patient Cases for Audit:** CTSU Audit Coordinators will work with the Group for selection of CTSU cases and particular data items to be audited. The Groups will receive a Pre-Audit Letter [*Exhibit 7.1.4*] approximately 8 weeks prior to the scheduled audit. The CTSU Audit Coordinators will follow the Internal CTSU Audit Communication Procedure [*Exhibit 7.1.5*]. The CTSU Audit Coordinators will review Group audits scheduled in AIS first. In addition, they receive CTMB AIS generated emails on a daily basis notifying them of scheduled Group audits.
   a) For case selection for all audits, CTSU requires a sampling stratification for 10% of Group cases, 10% of endorsed cases (where applicable) and 10% of non-endorsed cases (where applicable). These guidelines have been outlined by the CTMB. In any of the 10% calculations, the number of cases selected is standardized using the following guidance: if there are 11-20 cases, round up to 20.
   b) Selected non-endorsed cases are those cases enrolled via the CTSU at least 90 days prior to the scheduled audit date.
   c) If < 3 CTSU patients enrolled in non-endorsed studies are ***selected*** for audit at any one particular Cooperative Group member site, Cooperative Group auditors will audit CTSU cases per the Cooperative Group mechanism.
   d) If ≥ 3 CTSU patients enrolled in non-endorsed studies are ***selected*** for audit at any one particular Cooperative Group member site, CTSU auditors would augment the Cooperative Group audit team for the CTSU cases. Audit dates would be coordinated with the Cooperative Group Audit Coordinators.
   e) One unannounced CTSU patient case may be selected for limited audit on the day of the audit consisting at a minimum of review of informed consent and eligibility. However, if the unannounced cases only receive a limited review, then these cases do not count towards the number required for audit.

f) If the Group has a need for an additional CTSU Auditor to supply expertise in certain therapeutic area not addressed by the particular group, or if the Group feels there are other circumstances which would require additional audit support, the CTSU would be willing to consider supplementing the Group audit team on a case by case basis.

7. **Selection of Material for Review:** CTSU Audit Coordinators will work with the Cooperative Group Statistical Center sponsoring the protocol to provide copies of most or all CTSU submitted data forms to verify against the primary medical records. The submitted forms should include all data regarding eligibility and crucial outcome endpoints.
   a) IRB approvals, annual re-approvals and all required amendment approvals for all audited protocols are reviewed.
   b) A sample of at least 3 consent forms for at least three protocols will be carefully reviewed for all elements required by Federal Regulations. Of the 3 consent forms reviewed, one must be from a CTSU protocol.
   c) NCI Drug Accountability Record Forms (DARFs) for NCI-supplied agents will be reviewed where applicable. DARFs also will be crosschecked with at least 1 patient case for each of these drugs. One of the patient case DARFs reviewed must be from a CTSU case.

8. **Audit Preparation at the Institution:** The institution is responsible for ensuring that all relevant materials are available for review at the time of the audit. If affiliate institution records are audited at the time of the main member institution's audit, the affiliate institution must provide either the original patient source documents or copies of the complete record.

   a) This includes:
      - the Institutional Review Board (IRB) approvals, re-approvals and amendment approvals;
      - annual reports submitted to the IRB; and
      - the current version of the protocols, including any amendments and informed consents in use at the institution.
   b) Finally, all records regarding the disposition of investigational drugs, specifically copies of drug orders, return receipts, transfer forms, and the NCI DARFs, must be available. The pharmacy should be alerted that the auditors will conduct an on-site inspection of investigational agent storage and records.
      1. If the physician's office, clinic or other institution receives a ***multiple day supply*** of CTEP supplied investigational agents, satellite accountability records must be maintained for each satellite site and copies must be available for review by site auditors.
   c) The Principal Investigator, or his/her designee, and the research staff should be available throughout the audit to answer any questions and help the auditors locate necessary information in the source documents. The Principal Investigator must also participate in the Exit Interview.

9. **On-Site Audit Procedures Overview:** Auditors will review specific data related to research and regulatory requirements during the audit. Audit checklists will be utilized to assure that all elements are reviewed. Any problems or discrepancies found are noted on the checklist, and the document must be signed by the auditors and retained by the responsible Group.

10. **Review of Source Documents:** Source documents should be used to independently verify study data. Source documents may include, but are not limited to, the following:
    - Inpatient and outpatient medical records
    - Progress notes
    - Diagnostic reports (x-rays, scans, ECGs, etc.)
    - Laboratory data
    - Admission forms
    - Study flow sheets and Protocol or Study Roadmaps that are signed and dated
    - Appointment books
    - Enrollment tracking sheets
    - Subject diaries/calendars
    - NCI DARFS
    - Informed consents and IRB documents
    - Copies of study forms (case report forms) that are used as source documentation must be signed and dated.

11. **Assessment of Audit Findings:** Each of the 3 components (IRB/informed consent content, accountability of investigational agents and pharmacy operations; and individual patient case records) is assigned an assessment of either **Acceptable; Acceptable - Needs Follow-up, or Unacceptable,** based on findings at the time of the audit. Corrective Action Plans specific to the deficiencies identified are expected to be received from the site

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12. **Exit Interview:** At the conclusion of the visit, the audit team leader will conduct an exit interview with the responsible investigators and all other appropriate staff. During this exit interview, the preliminary findings and any recommendations from the audit team will be discussed. This interview provides opportunity for education, immediate dialogue, feedback, and clarification. The audit team leader should document the discussion in detail. This will facilitate the submission of appropriate information for the AIS final audit report to CTMB. The Principal Investigator must participate in the exit interview process.

13. **Reporting Requirements:** One single Audit Report is required for each audit performed. The Group audit team leader must fax a Preliminary Audit Report of audit findings within one working day of completing the audit to the CTMB [*Exhibit 7.1.6*].

    a) If the audit is for CTSU to CTSU enrollment, the CTSU Auditor must fax a Preliminary audit report to CTMB within one working day. If the audit is for CTSU to Group

enrollment, the Group Auditor must fax a Preliminary audit report to CTMB within one working day.

b) Any major deficiencies discovered during the audit must be described in the Preliminary Report. Any findings that are suggestive of intentional misrepresentation of data, and/or disregard for regulatory safeguards for any of the three components of the audit, must be reported to the CTMB immediately by telephone at (301) 496-0510.

c) Utilizing the audit findings provided by the audit team, the Group Audit Coordinator will enter final audit information for all enrollment into the CTMB AIS within 70 working days of the audit date.

d) If the audit is for CTSU to CTSU enrollment, the CTSU Auditor will enter the final audit information for all enrollment into the CTMB AIS within 70 working days of the audit date. Once the Audit Report is finalized in AIS, the Audit Coordinator will provide a copy of the audit report to the audit site and the Cooperative Group sponsoring the protocol [*Exhibit 7.1.7*]). CTSU will receive notification that the final report has been completed on CTSU protocols. CTSU will review the audit report that contains only CTSU protocols and details displayed.

14. **Follow-up Requirements:** For **each** component rated as **Acceptable - Needs Follow-up** or **Unacceptable,** the institution is required to submit a written response and/or corrective action plan to the audit coordinator within four weeks of the date the Final Report was mailed. A copy of the written response/corrective action plan, along with an assessment by the coordinating Cooperative Groups of the response/corrective action plan, is forwarded to CTMB within 45 days of the date the final audit report was entered into the CTMB AIS.
    a) A re-audit (either internal and/or on-site) is mandatory for any component rated as unacceptable.
    b) The CTSU reserves the right to conduct a re-audit of any of the CTSU patient cases, pharmacy and/or regulatory materials that are rated as unacceptable.

VII. DOCUMENTATION REQUIREMENTS

1. The following documents are required as part of the audit documentation process :
    - Pre-Audit Letter to the Principal Investigator at the site announcing the date of the audit, a list of the patients and protocols to be reviewed and a description of all of the materials that must be available for review.
    - Preliminary Audit Report of audit findings must be faxed to CTMB within one working day of completing the audit.
    - Final Audit Report must be created in the CTMB AIS within 70 working days of the audit date.
    - Post–Audit Letter describing the audit findings and requesting a written response/corrective action plan for all categories labeled Acceptable Needs Follow-Up or Unacceptable will be mailed along with the Final Audit Report to the site.
    - Written Response/Corrective Action Plan must be submitted by the site to the Audit Coordinator within four weeks of the date the Final Audit Report was mailed.
    - When indicated, a Follow-Up Letter will be sent to the site (copy to CTMB) after review of items contained in the Written Response/Corrective Action Plan such as challenges to audit findings

with supporting documentation provided or items that may require clarification or additional documentation.